REMARKS

Applicants respectfully request entry of amendments to claims 1, 5-9, 12-15, 18-20, 22, 26, 32-36, and 39-41, adding new claim 42 and canceling claims 3, 4, and 27-30, without prejudice or disclaimer. Claims 31 and 37 are withdrawn from consideration. Support for the amendments can be found throughout the specification, including p. 5, ll. 20-24, and p. 19, ll. 18-19, and the originally filed claims and, therefore, do not add new matter.

Applicants submit that pending claims 1, 2, 5-26, 32-36, and 38-42 are in condition for allowance, and respectfully request that the claims as amended be entered.

Objections

The Office Action alleges that new corrected drawings in compliance with 37 C.F.R. §1.121(d) are required because the data appear to be incorrectly graphed. Applicants respectfully submit that the Action demonstrates a profound misunderstanding of how ischemia/normal blood flow ratios are typically represented in graphic form.

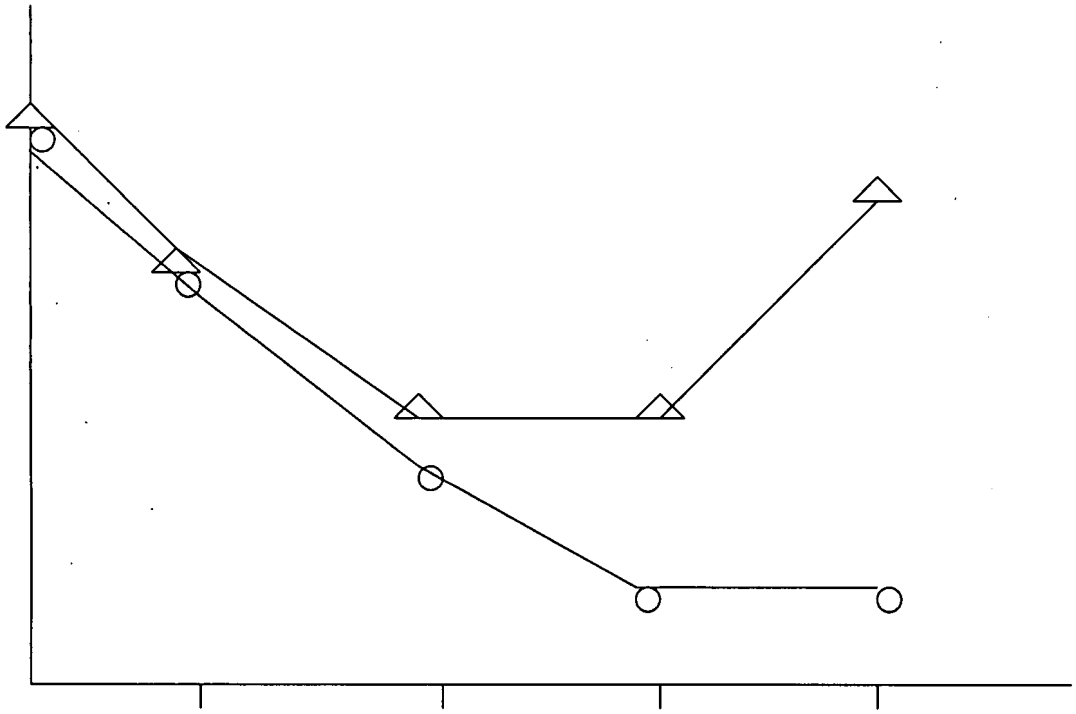
As described in the Examples of the specification, the ischemia animal model used to assess the test agents involved a unilateral surgical resection of the femoral artery creating an animal with one hind limb with ischemic blood flow and one hind limb with normal blood flow. The ratio of "ischemic/normal blood flow" in the Figures is a comparison of the blood flow in the ischemic limb compared to that in the normal limb.

Applicants offer the following simplified example for a fictitious efficacious agent:

Two animals: A = control (circles) B = treated (triangles).

Animal B is treated with an agent and the other animal, A, is untreated; the left legs (L) of both animals are surgically modified such that blood flow is occluded; and the right legs (R) are unmodified, such that blood flow is maintained (i.e., normal). At t_0, the ischemic/normal blood perfusion ratio from the legs of each animal has a value of 1.0, i.e., the ratio for the left leg to the right leg of each animal before treatment is $L/R_{AB} = 1.0/1.0$. At t_1, where there may be no effect on the treated animal at this point, the flow in the left leg relative to the right leg will be reduced in both animals; i.e., the ratio will drop: $L/R_{AB} = 0.9/1.0$. At t_2, there may be some effect of the treatment, where overall effect is that the left leg flow is less than the right, but this

difference between legs is less in the treated animal B; i.e., $L/R_A = 0.8/1.0$ v. $L/R_B = 0.85/1.0$. At t_3, there is a significant effect on blood flow in the treated animal versus the control; i.e., the treated animal stabilizes and the untreated animal's flow rate continues to drop: i.e., $L/R_A = 0.5$ v. $L/R_B = 0.85$. At t_4, the treatment results in restoring original blood flow ratio, while control flow continues to drop: i.e., $L/R_A = 0.45$ v. $L/R_B = 1.0$. Graphically, these data can be represented as follows:



t_0 t_1 t_2 t_3 t_4

Y axis is Ischemic/Normal Blood Perfusion Ratio

X axis is time after treatment

This simplistic illustration represents how such data is typically graphed. Further, Applicants have provided a copy of a reference where ischemia has been investigated, and a similar graphic representation of the ratio data is disclosed (see, e.g., Duan et al., Circulation, (2000) 102:370-376, at page 373, Figure 2B). Therefore, as ischemic/normal blood perfusion

ratios are typically presented as illustrated in the figures as filed, figures 4, 8, 14, 20, and 25 are in compliance with 37 C.F.R. §1.121(d).

Regarding the mis-numbering in Figure 25, this has been corrected.

Claims 1, 35, and 36, including claims dependent therefrom, are alleged to contain informalities related to the use of acronyms. While not acquiescing to the reasoning offered in the Action, and to expedite prosecution towards allowance, the claims have been amended to recite the full spelling of the term followed by the abbreviation in parentheses in the first appearance of the word/term.

For these reasons, Applicants respectfully request that the objections be withdrawn.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 12-21 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Claims 12-17 no longer recite "reference eNOS polypeptide" so the rejection is rendered moot. Applicants have amended the claims to recite "wild-type eNOS polypeptide." The term "wild-type" is a term of art and would be known to one of skill in the art generally as the non-mutated form of a gene or gene product. As such, one of skill in the art would understand the metes and bounds of the term.

Regarding claims 18 and 19, while Applicants do not acquiesce to the reasoning offered in the Office Action, and to expedite prosecution toward allowance, claims 18 and 19 have been amended to no longer recite the disputed terms.

Regarding claims 20 and 21, while Applicants do not acquiesce to the reasoning offered in the Office Action, and to expedite prosecution toward allowance, claims 20 and 21 have been amended to no longer recite the disputed term.

For these reasons, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-30, 32-36, and 38-41 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description support. As claims 3, 4 and 27-30 have been canceled, the rejection as applied to these claims is rendered moot.

Applicants traverse the rejection as it might apply to the amended claim, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that as the specification does not disclose a "representative number of the genus[sic], nor does it provide a descriptive[sic] of structural features that are common to the genus" the claims do not meet the standard for adequate written description. Applicants respectfully submit that such allegations are incorrect.

Notwithstanding the amendments to the claims, it is not clear as to how the Action has come to this position, as the positions which are disclosed in the specification for mutation are well known in the art, and are relatively constant across species. For example, Applicants have provided sequence data for at least five species of eNOS (i.e., bovine, rat, mouse, pig, and human; Exhibit A), which includes region and site data for equivalent positions for calmodulin modulation and phosphorylation. Further, Applicants have provided BLAST 2 comparison sequence data comparing each of the sequences identified above, where the BLAST 2 analysis shows between 93 and 94% identity when comparing the animal protein sequences for eNOS with human eNOS protein sequences (Exhibit B).

Nevertheless, the position taken in the Office Action in view of the cited case law is inapposite in that none of the cases recited in the Action support a written description standard which requires a re-description of what was already known. For example, in Regents of University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), the court stated that "naming a type of material generally known to exist, in the absence of knowledge as to what the material consists of, is not a description of that material." In Lilly, the sequence for cDNA encoding human insulin *was unknown*, and the specification only described rat insulin. Further, in Fiers v. Revel, 25 U.S.P.Q.2d 1601, 1604, 984 F.2d 1164, at 1171 (Fed. Cir. 1993), much of the DNA sought to be claimed *was of unknown structure*, whereby the court viewed the breadth of the claims as embracing a "wish" or a research plan. In Amgen Inc. v.

Chugai Pharmaceutical Co., Ltd., 18 U.S.P.Q.2d 1016, 1021, 927 F.2d 1200, at 1206 (Fed. Cir. 1991), the court explained that *a novel gene* was not adequately characterized by its biological function alone because such a description would represent a mere "wish to know the identity" of the novel material. In Fiddes v. Baird, 30 U.S.P.Q.2d 1481, at 1483 (Bd. Pat. App. & Int. 1993), the court explained that the state of the art at the time the invention was filed, where the inventor only disclosed an amino acid sequence and *a theoretical DNA sequence*, there was inadequate knowledge concerning the relationship between gene structure and proteins for the theoretical sequence to be used to establish possession. For the instant invention there are no theoretical sequences, and the sequences disclosed in the instant specification are already known, including recognized structure/function relationships between recited genes and their corresponding encoded proteins/domains for humans as well as other mammalian sequences. Thus, the present facts are distinguishable.

On the other hand, in Capon v. Eshhar, 76 U.S.P.Q.2d 1078, 1085, 418 F.3d 1349, at 1357 (Fed. Cir. 2005), the court stated that requiring sequences to be fully presented, although the sequences of the component genes are known, is an inappropriate generalization. The court reasoned that when the prior art includes sequence information, there is no *per se* rule that the information must be determined afresh. Id. As in Capon, the present invention is not in the discovering of which segments of some unknown or "wished for" sequence might be related to a specific function, but in the novel use of and manipulation of art recognized functional positions of known genes to achieve a novel result (Id., at 1357). Thus, in concurrence with the Court of Appeals for the Federal Circuit in Capon, Applicant submits that the requirement that a method using mutant eNOS polypeptides prepared from known sequences of known function must be analyzed and reported in the specification is not the standard for written description. Id.

The claims as presently recited describe eNOS polypeptides with particular mutations. Wild-type eNOS homologs and other eNOS mutations are described in the specification and well known and well described in the art. As such, one of skill in the art could envision the chemical details of the eNOS mutants of the claimed invention. The specification in combination with that known in the art provides a description of sufficient, relevant, identifying structural and functional characteristics of the mutant eNOS polypeptides to adequately describe possession of

the claimed genus to one skilled in the art. Thus, the pending claims are fully described in the specification as filed. Accordingly, Applicants respectfully submit that the written description requirement has been met.

For these reasons, Applicants respectfully request that the rejection be withdrawn.

Claims 1-30, 32-36, and 38-41 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. As claims 3, 4 and 27-30 have been canceled, the rejection as applied to these claims is rendered moot.

Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that while the specification is enabling for a method of treating critical limb ischemia (CLI) comprising administering by intramuscular injection to a patient in need of treatment of an effective amount of a recombinant adenovirus comprising a polynucleotide encoding a mutant mammalian endothelial nitrogen oxide synthase (eNOS) polypeptide, does not reasonably enable the genus for a) methods of administration and b) methods of polypeptides encoding normal and mutated mammalian eNOS polypeptides.

As the amended claims recite "intramuscular ," this aspect of the rejection is rendered moot. Further, as the amended claims recite "mutant eNOS," the claims no longer embrace normal or wild-type eNOS. So this aspect of the rejection is also rendered moot.

However, with regard to whether the claims must be limited to the scope as recited in the Action, Applicants respectfully submit that such a limited scope is inappropriate given the teachings in the specification and what was known in the art at the time the invention was filed.

While it is appropriate to recognize variability in determining the scope of invention, determination of what is needed to support generic claims to biological subject matter depends on a variety of factors including 1) knowledge in the particular field, 2) the extent and content of the prior art, 3) the maturity of the science or technology, and 4) the predictability of the aspect at issue. Capon v. Eshhar, 76 U.S.P.Q.2d 1078, 1084, 418 F.3d 1349, at 1356 (Fed. Cir. 2005).

The present invention represents more than "a mere germ of an idea," the specification supplies the novel aspects of the invention and describes the study of eNOS in vascular related

investigations (e.g., p. 2, ll. 18-32). (See, also, Genentech, Inc. v. Novo Nordisk, 42 U.S.P.Q.2d 101, 108 F.3d 1361 (Fed. Cir. 1997)). Further, in the present specification, not only are the general teachings of how to select the requisite polypeptides disclosed (e.g., p. 13, ll. 21-37; p. 14, ll. 17-25; p. 19, l. 5 bridging to p. 21, l. 28), but also specific examples are provided for the production of eNOS polypeptides containing multiple mutations (e.g., p. 29, ll. 30-37; p. 30, ll. 17-28; p. 32, ll. 17-20 and 35-37). Moreover, standardized description and identification, including known procedures for selecting, isolating, and linking known DNA segments containing well recognized domains, whose structure/function relationships are known, are disclosed (e.g., p. 13, l. 21 bridging to p. 29, l. 17). And while such procedures involve some level of technical manipulation, because such methods and steps are routinely used in the art, such procedures do not rise to the level of undue experimentation. (See, e.g., Johns Hopkins University v. Cellpro, Inc., 47 U.S.P.Q.2d 1705, 152 F.3d 1342 (Fed. Cir. 1998), where the court stated that "experimentation does not constitute undue experimentation" where "it is merely routine.").

Regarding unpredictability, it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize the generic invention. See, e.g., In re Angstadt, 537 F.2d 498, 504 (CCPA 1976). Accordingly, generic inventions are not *per se* invalid because success for each possible iteration is not assured. Capon, at 1357.

The specification provides adequate guidance to enable one skilled in the art to make and use the claimed invention. Regarding the Wands factors, 1) sequence information for eNOS for humans and other species are provided in the specification and the prior art, including structure and function data for specific sites on eNOS; 2) the specification discloses the requisite positions of the mutated residues comprising the mutant eNOS polypeptides (see, e.g., Figure 1) and specific residues comprising mutant polypeptides are art recognized, including structure/function relationships,; 3) as stated above, eNOS in vascular related studies is certainly not in the early stages of investigation (e.g., p. 2, ll. 18-32); 4) the level of skill in the art is high, and such a skilled artisan would have the knowledge and capabilities of using the information provided in the specification to make and use the invention commensurate in scope with the amended claims

(e.g., search sequence databases, use standard cloning techniques to operably link DNA sequences, produce recombinant proteins from eukaryotic hosts comprising expression vectors, etc.); 5) the specification provides examples of expressing various mutations, including multiple mutations (see, Examples 2 and 3); 6) as stated above, standardized description and identification, including known procedures for selecting, isolating, and linking known DNA segments, including recombinant expression vectors, containing well recognized domains, whose structure/function relationships are known, are disclosed (e.g., p. 13, l. 21 bridging to p. 29, l. 17); 7) at least 3 working examples of the method of modulating eNOS in vivo with administered mutant and/or modified eNOS (e.g., "knock out") are disclosed; and 8) as stated above, the procedures used to practice the invention are merely routine (e.g., see Example 1), and such procedures do not rise to the level of undue experimentation.

Therefore, the claims are enabled because the specification provides appropriate guidance, working examples, and prediction of function based on observed properties of the claimed polypeptide such that one of skill in the art could practice the invention as claimed, in the absence of undue experimentation. Thus, the pending claims are in compliance with the enablement requirements.

For these reasons, Applicants respectfully request that the rejection, including as it may be applied to the amended claims, be withdrawn.

Rejection Under 35 U.S.C. §103

Claims 1, 2, 4, 6, 10, 12, 13, 15-18, 20-26, 32, 34-36, and 39 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Smith et al in view of Fulton et al. Applicants respectfully traverse this rejection. As claim 4 has been canceled, the rejection as applied to this claim is rendered moot.

Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First there must be some suggestion or motivation in the references themselves or in knowledge generally available to one of skill in the art, to modify the reference or combine the reference

teachings. Second, there must be a reasonable expectation of success. And, finally the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion and reasonable expectation of success must both be found in the prior art and not in Applicants' disclosure. (See M.P.E.P. §706.02(j)). If any one of these three criteria is not met, a *prima facie* case of obviousness has not established.

As amended, the claimed methods comprise administration of a polynucleotide encoding a mutant eNOS polypeptide wherein the eNOS polypeptide comprises at least one mutation at a position that is phosphorylated in wild-type eNOS in mammalian cells, the position being in the calmodulin-binding domain corresponding to amino acid residues 478-522 of SEQ ID NO:1. Applicants submit that neither Smith et al. nor Fulton et al., alone or in combination, teaches or suggests the use of a polynucleotide encoding a mutant eNOS polypeptide as claimed. Thus, the cited references do not teach or suggest the claimed invention.

Further, Applicants submit that because the cited references do not teach all the claim limitations, one of skill in the art would not be motivated to combine the reference teachings.

The Office Action alleges, in pertinent part, that Smith et al. is silent with respect to teaching a method for treating CLI comprising the administration of an adenovirus encoding a mutant mammalian eNOS polypeptide. The Action then provides Fulton et al. to cure the deficiency identified in the primary reference. However, review of Fulton et al. shows that the mutant as described is an eNOS with mutation at serine 1177 with the calmodulin-binding domain intact. The combination of Smith et al. and Fulton et al. would not achieve the invention as claimed; i.e., a method of treatment with a mutant eNOS as claimed. Therefore, one of skill in the art would not be motivated to combine such teachings.

Finally, because the teachings of Smith et al. would not result in the invention as claimed when combined with the teachings of Fulton et al., one of skill in the art would not have an expectation of success since the invention as claimed would not be achieved in view of such teachings.

Again, the "teaching or suggestion and reasonable expectation of success must both be found in the prior art.". One cannot simple use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774

Conclusion

Applicants submit that pending claims 1,2, 5-26, 32-36, and 38-42 are in condition for allowance. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this submission.

A check in the amount of $1020.00 is enclosed to cover a Three Month Extension of Time fee. No other fee is deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees required by this submission, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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